JANSSEN
PHARMACEUTICA
Naamloze Vennootschap

Dockets Management Branch (HFA-305)
Food and Drug Administration
5630 Fishers Lane, Room 1061
Rockville, Maryland 20852
U.S.A.

Beerse, March 31, 1999.

Re: Docket No. 98D-0994; Draft Guidance for Industry on BACPAC I – Intermediates in Drug Substance Synthesis. Notice of Availability in the Federal Register of November 30, 1998 (Vol. 63, No. 229, page 65793).

Dear Sir/Madam,

Janssen Pharmaceutica N.V. in Belgium, as a member of Johnson & Johnson family of companies, manufactures a high number of Active Pharmaceutical Ingredients and intermediates. Many of these APIs are marketed as Drug Products on the U.S. market through J&J and through non-J&J companies. The chemical manufacturing & control information to support the NDAs is filed with the FDA as type II Drug Master Files.

As a directly impacted party, we are pleased with the development of initiatives like BACPAC, which will provide very clear guidance on the classification of post approval changes and the associated documentation and communications to the Agency. We are even more pleased with the opportunity to provide comments, and to be able to contribute in the development of such guidance documents.

The proposed BACPAC-I guidance document in general is already a high quality document, and clearly the result of thorough analysis of the complex matter of change management. We have extensively reviewed the document, and would like to submit our comments (see attachment).

98D-0994

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Janssen Pharmaceutica N.V. – Belgium
Comments on Draft FDA Guidance
BACPAC I: Intermediates in Drug Substance Synthesis (Docket No. 98D-0994)

General comments

It is our understanding that BACPAC-I covers changes in the information filed in the approved application(s), as intended by 21 *CFR* 314.70(a), and is not covering changes in equipment or other parameters that were not specified in the application(s). This should be clearly defined in the document.

The guidance contains sufficient detail that regulatory decisions are now much clearer for post-approval changes made in early synthetic steps. The general approach of comparing the equivalence of material pre- and post-change represents a rational, scientific method for evaluation of the impact of a given change. The filing requirements in the draft guidance generally reflect the results of this evaluation, and provide some regulatory relief from current 21 *CFR* 314.70 requirements. Significant benefit to industry is also achieved through the ability to demonstrate equivalence based on impurity profile at synthetic intermediates after the change, without always requiring evaluation of the API (including physical properties or stability).

However, Janssen feels that BACPAC-I still requires too much the use of CBEs for process changes in early steps of the synthesis. If the change occurs prior to the final intermediate and there is no change in impurities at or before the level of the final intermediate, the filing should always be an annual report (except changes to an unapproved site). The document clearly recognizes the fact that when there are no changes in the impurity profile at or before the final intermediate, it is almost impossible to affect the physico-chemical quality characteristics of the API or Drug Products. We consider this to essential to provide real regulatory relief, because for a type II DMF there is no mechanism for CBE without an update of each NDA that may be affected.

We have some difficulty with the fact that it is generally accepted that the degree of GMP controls should increase towards the end of the synthesis chain (Guide to Inspection of Bulk Pharmaceutical Chemicals), versus the finding that BACPAC-I does not differentiate in this respect. For most older processes, and especially for the very early synthesis steps, analytical methodology is not available for full characterization of the impurity profiles of these synthetic intermediates. In such cases, the development and validation of adequate analytical methods for quantifying existing and new impurities may be considered too costly to take advantage of the regulatory relief offered by evaluation of changes at process intermediates.
To our understanding, the current ICH thinking is to define an "API Starting Material" one or two synthesis steps before the final intermediate, as the starting point of full GMP control. We would like to propose the introduction of a similar concept into BACPAC-I, meaning that for changes before that "API Starting Material" a sound scientific support based on laboratory experiments and full scale confirmations should be sufficient, without formal validations.

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An area of concern is the level of documentation requested in support of changes. In some areas, the required detail in data and information is greater than what is provided in original applications (NDAs). It is the experience of Janssen companies that analytical methods for raw materials and intermediates are briefly summarized and no accompanying validation data is provided in original NDA filings. Detailed method and/or process validation data are required under GMP, and should be available for inspection, but are not necessarily part of any regulatory filing. The requirement of certificates of analysis for raw materials and starting materials is another example of additional detail not typically provided in new applications. A batch data summary for the relevant materials should meet the requirement. Similarly, for the redefinition of an intermediate as a starting material, the list of sources and the change-control protocol can be considered GMP considerations that should not be included in a filing.

The requirement to demonstrate equivalence of pre-change (10 batches) and post-change (3 batches) material is clearly stated in BACPAC-I. However, for certain low volume or recently approved APIs, the manufacturing history may not cover 10 commercial scale batches, while sufficient supporting information may be available from development work (be it from quality of intermediates used in manufacturing of clinical batches, be it from development work to support the change). In such cases, justification of the change based on development information, with confirmation through pilot scale batches and/or at least one full scale batch, should be allowed, as an alternative to proving equivalence on a statistical basis. Also, where limits have been approved for specific impurities in an intermediate, meeting these limits would demonstrate equivalence.

On several occasions, BACPAC-I requires equivalence of impurity profiles, including residual solvents. Residual solvent content is relevant at the level of APIs, not at the level of intermediates which undergo further chemical modifications up to the crude API. The final crystallization solvent is determining for the residual solvent content in the API. Because of this, it is not the current industry practice to test intermediates for residual solvents. Also, to our opinion, the reference to ICH Q3C, Option 1 is meaningless since the proposed values are based on a theoretical daily dose, which does not exist for an intermediate.
We propose to remove the residual solvent requirements from BACPAC-I, and to include changes in residual solvent into BACPAC-II, at the level of APIs.

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Specific Comments

I. Introduction

Line 16: Analytical method changes at the level of the final intermediate are covered under BACPAC-I. Since these changes can result in a change in final intermediate's specifications, we suggest to include these specification changes also in BACPAC-I.

III. Assessment of change

Line 95-96: Isomers may be present in a drug substance as low level isomeric impurities. A change result in a decrease in the level of the undesired isomer, which is an improvement. When isomeric composition of the API is important, it should be part of the specifications. Therefore we suggest to require meeting the API specifications on chirality.

III. A. Equivalence of Impurity Profiles

- Line 129: It is suggested that the demonstration of equivalence may also take place at an *in situ* intermediate if appropriate justification is present, meaning adequate analytical methodology is available).

- Line 137: Suggested to modify, to include any specifications for specific impurities that have been filed for an intermediate: "existing impurities are within the stated limits or, if not specified, at or below the upper statistical limits of historical data". See our general comment on residual solvents in intermediates.

- Line 139: Suggested to modify to include any specification for total impurities that has been filed for an intermediate, similar to the comment above.

- Line 159: See our comment on line 129.

III.B Equivalence of physical properties – line 178 on

- The basis for deciding on the need to evaluate equivalence of physical properties of the API should be extended to include the quality profile of the material that goes into the final crystallization step. This is usually not the final intermediate, but the crude API that is obtained after chemical reaction of the final intermediate.

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IV.A Site, scale and equipment changes

- Line 209...: this recognises the need to slightly change process parameters when moving to other equipment, and also confirms the expectation that such changes will generally not result in different impurity profiles.
  Scale changes (will generally also require slight modifications in parameter settings (e.g. addition times, heating/cooling times...). Scale changes may be filed as annual report.

  This conflicts with the statements on manufacturing process changes (line 406: process parameter changes are taken together with solvent, reagent, purification procedure changes). The requirement for such changes is to file as CBE.
  So far, in our communications and submissions of amendments to DMFs/Annual reports to NDA's, process parameter changes have always been accepted as annual report items.
  We feel it to be very important to leave process parameter changes out of IV.C, and take them into IV.A, or make a separate chapter IV."x" on "process parameter changes", where, when equivalence is demonstrated, the filing should be annual report.

- Since scale changes are generally connected to other changes (equipment, site changes), there is no need to specifically address scale changes in BACPAC-I.

IV.B Specification Changes

Line 354 and line 395: If the only change made is a specification change, then reporting by Annual Report is considered appropriate. If another type of change were also made, then evaluation of equivalence would need to be demonstrated and the designated filing mechanism used.

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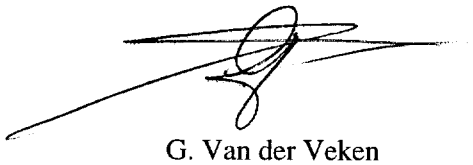
We are looking forward to future opportunities to co-operate, not only BACPAC II, but also any other guidance document that might impact on API manufacturing & control.

Sincerely



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BRIEF

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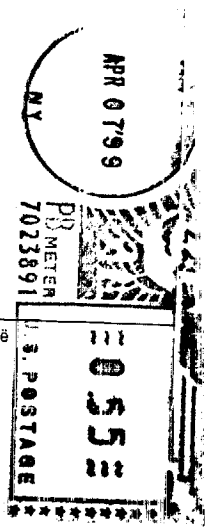

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